

ORIGINAL ARTICLE

Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection

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Abstract

Background: Intrahepatic recurrence is a significant problem for patients who have undergone a hepatic resection for hepatocellular carcinoma (HCC). The objective of the present study was to identify risk factors and evaluate the management of early and late recurrence of solitary HCC after curative resection.

Methods: Included in this study were 816 patients with solitary HCC who underwent a curative partial hepatectomy. Intrahepatic recurrence in these patients was followed up retrospectively. Prognosis and therapy for the recurrence were investigated and analysed.

Results: Early and late intrahepatic recurrence occurred in 423 patients and 199 patients, respectively. Multivariate analysis showed that a tumour diameter >5 cm, the absence of a tumour capsule and the presence of microvascular invasion were correlated with early recurrence, whereas cirrhosis and alpha-fetal protein >400 µg/l were independent risk factors contributing to late recurrence. The 5-year survival of HCC patients with early recurrence was significantly lower than that of patients with late recurrence. Further curative treatment for intrahepatic recurrence offered a 5-year overall survival of 56.0%, which was better than alternative management.

Conclusion: Early and late recurrences of solitary HCC after curative resection are associated with different predictive factors. The time to recurrence and further curative treatment after recurrence were the best predictors of survival post recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and leading causes of cancer-related death worldwide.¹ Surgical treatment options for HCC include PH (partial hepatectomy) and LT (liver transplantation).² Theoretically, LT is the therapeutic gold standard in cirrhotic HCC patients who meet the Milan criteria because it can remove all the

intrahepatic tumour foci together with the oncogenic cirrhotic liver.³ Because of the shortage of donor organs and a long waiting time, primary PH remains the first-line treatment for HCC patients or serves as a bridge for future salvage LT.⁴ Unfortunately, PH is associated with a high risk of post-operative intrahepatic recurrence that occurs in about 80% of HCC patients at 5 years and is the leading cause of post-operative death.^{5–9} Therefore, it is essential that risk factors of recurrence be determined and a strict follow-up protocol as well as treatment strategies be established for early detection and intervention of recurrence.

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Previous studies reported that early recurrent tumours most likely originated from subclinical metastasis of primary tumours, whereas late recurrent tumours might be multicentric or *de novo* primary HCC in the remnant liver.^{10–12} Different risk factors are considered to be involved in each type of recurrence. Increasing tumour stage, the presence of microsatellite and microvascular invasion (MVI) and an elevated alpha-fetoprotein (AFP) level have been reported to be associated with early recurrence, whereas cirrhosis, multinodularity and hepatitis activity have been shown to be predictors of late recurrence.^{5,10,13} However, in most of these studies, the enrolled patients were heterogeneous in terms of clinicopathological characteristics and management-related factors. Various studies have produced conflicting results concerning factors predicting recurrence, and few previous studies have focused on risk factors for intrahepatic recurrence in an exclusive cohort of patients with solitary HCC after curative PH.

The aim of this study was to identify prognostic factors influencing post-operative recurrence and survival of patients undergoing curative PH for solitary HCC.

Materials and methods

Enrolled in this study were 918 consecutive patients who had undergone curative PH for solitary HCC at the Eastern Hepatobiliary Surgery Hospital (Shanghai, China) between March 2000 and September 2010. The pre-operative clinical diagnosis of HCC was consistent with the diagnostic criteria of the American Association for the Study of Liver Diseases (AASLD).¹⁴ Patients who met the following criteria were included in this study: pre-operative World Health Organization performance status of 0–1; Child–Pugh class A; only one hepatic lesion; no extrahepatic metastases; no image-visualizable tumour thrombus in the portal vein, hepatic vein or bile duct branches; and suitable for curative PH.

The surgical strategy for HCC was standardized for all patients. Curative resection of HCC was performed as described previously.¹⁵ In brief, the whole tumour was resected with a negative surgical margin confirmed by histological examination; the pre-operative elevated AFP level decreased to the normal range within 2 months after surgery; and no new image-visualizable intra- and extrahepatic lesions within 2 months after surgery. Patients who underwent palliative resection and/or adjuvant therapy after a hepatectomy, or died owing to severe complications within 1 month after surgery were excluded from this study. This study was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital.

The diagnosis of HCC was confirmed in all patients by pathological evaluation of the surgically resected specimens. The histological grade of tumour differentiation was assigned by the Edmondson–Steiner's classification system.

Clinicopathological factors that were potentially related to recurrence included age, gender (male or female), serum hepa-

titis B surface antigen (HBsAg) status (positive or negative), hepatitis E surface antigen (HBeAg) status (positive or negative), cirrhosis (presence or absence), AFP level (≤ 400 or > 400 $\mu\text{g/l}$), prothrombin time (PT) (≤ 13 or > 13 s), platelet count (PLT) (≤ 100 or $> 100 \times 10^9/\text{l}$), total bilirubin (TBIL) (≤ 17.1 or > 17.1 $\mu\text{mol/l}$), albumin (ALB) (≤ 35 or > 35 g/l), alanine aminotransferase (ALT) (≤ 50 or > 50 U/l), hepatitis B virus (HBV)-DNA (≤ 4 or > 4 lg, IU/ml), intra-operative blood transfusion (yes or no), surgical margin (< 2 or ≥ 2 cm), anatomical PH (yes or no), tumour diameter (≤ 5 or > 5 cm), tumour capsule (yes or no), MVI (yes or no), and Edmondson–Steiner's classification (I/II or III/IV).

All patients were followed up regularly every 2 months during the first 2 years, and 3 months afterwards, and monitored by a standard protocol including serum AFP, immunological indexes of HBV, liver function, abdominal ultrasound or contrast-enhanced computerized tomography (CT)/magnetic resonance imaging (MRI) and chest X-ray. All patients were followed up until September 2013.

Once recurrence was suspected based on the combined results of these clinical examinations, patients were hospitalized and treated with curative treatments including re-resection, percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA) when the recurrence was localized, or otherwise with transcatheter arterial chemoembolization (TACE) or conservative management with sorafenib when the recurrence was diffuse. Time to recurrence (TTR) was defined as the period between surgery and the diagnosis of recurrence by setting 2 years as the cut-off between the early and late recurrences.^{5,13,16} The overall survival (OS) time was defined as the interval between PH and death or between PH and the last follow-up. Patients who died for reasons not related to HCC were censored at the time of death.

Statistical analysis

Continuous variables were reported as the median and range. The cut-off values of the continuous variables were based on those used commonly in previous studies or as determined by maximizing the Youden's index, i.e. sensitivity + specificity - 1, as calculated from the receiver-operating characteristic curve (ROC).¹⁷ The χ^2 test or Fisher's exact probability test was used for categorical variables. The cumulative survival time was calculated using the Kaplan–Meier method and compared by the log-rank test. The Cox proportional hazards model was used to determine independent factors of recurrence based on the variables selected by univariate analysis. All the significant predictors of recurrence in the univariate analysis were analysed in a logistic regression model to show an independent value at the multivariate analysis. Statistical analyses were performed by SAS 9.1.3 software (SAS Institute Inc., Cary, NC) and R 2.13.2 (<http://www.r-project.org/>). A two-tailed value of $P < 0.05$ was considered statistically significant.

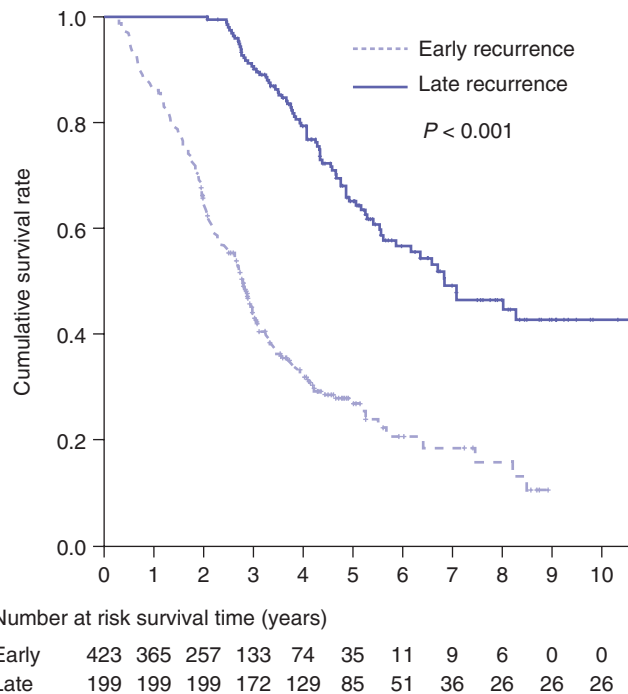


Figure 1 Long-term survival from the diagnosis of intrahepatic recurrence according to time of presentation (earlier or later than 2 years)

Results

Of the 918 patients 102 (11.1%) patients were excluded.

The median follow-up time was 53 (18–104) months; the median OS time was 62 months; and the 1-, 3- and 5-year recurrence and OS of these patients was 25%, 64%, 75%, 90%, 65% and 51%, respectively. Of the 816 patients in this series, 622 (76%) patients developed intrahepatic recurrence, of whom 423 (423/622, 68%) patients experienced recurrences within the first 2 years (early recurrence) and 199 (199/622, 32%) after 2 years (late recurrence). In the non-recurrence group, the 5-year OS was 85% versus 38% for all patients who recurred ($P < 0.001$). The 5-year OS in the late recurrence group was significantly higher than that in the early recurrence group (59% versus 28%, $P < 0.001$) (Fig. 1).

Univariate and multivariate analysis of risk factors for both early and late recurrence are shown in Tables 1 and 2.

Therapy and prognosis after recurrence

Of the 423 patients in the early intrahepatic recurrence group, further curative treatment was performed in 135 (32%) patients, including re-resection ($n = 97$, 23%), PEI ($n = 13$, 3%) and RFA ($n = 25$, 6%). Of the 199 patients in the late intrahepatic recurrence group, further curative treatment was indicated in 91 (46%, $P = 0.039$) patients, including re-resection ($n = 61$, 31%), PEI ($n = 9$, 5%) and RFA ($n = 21$, 10%).

After recurrence, the 1-, 3- and 5-year OS of the 236 patients who received further curative treatment was significant greater than the 393 patients who did not receive further curative treatment (96%, 70% and 56% versus 82%, 47% and 28%, $P < 0.001$). Furthermore, The 1-, 3- and 5-year OS of patients who received TACE for recurrence was significant better than that of patients who received conservative management with Sorafenib after recurrence (86%, 51% and 34% versus 69%, 35% and 9%, $P < 0.001$), but lower than that of patients who received further surgical curative treatment for recurrence ($P = 0.030$). There were no significant differences in OS among the patients who received re-resection, RFA and PEI after recurrence.

Discussion

In the present study, risk factors and management for early and late recurrence of solitary HCC based on a large cohort of patients who underwent curative PH were assessed. The results show that early recurrence is a major problem after curative PH even in patients with solitary HCC.

Previous studies^{13,18} suggest that intrahepatic metastases are the main cause of early intrahepatic recurrence. In the present study, results confirmed that early was associated with adverse tumour factors, such as larger tumour size, MVI and the absence of a tumour capsule, as reported previously.^{19–21} The high early recurrence rates seen in HCC patients with these characteristics suggest that there may be microscopic intrahepatic dissemination beyond the resection field in such patients and therefore simple tumour removal would seem insufficient.²²

Liver cirrhosis has been considered to be the only risk factor related to late recurrence in patients with HCC after PH.^{13,16} Cucchetti *et al.*¹¹ reported that the risk factors for late recurrence in cirrhotic HCC patients are the same as for HCC occurrence in the general cirrhotic population, confirming the hypothesis that late recurrence is to be considered multicentric HCC. In this study, cirrhosis was also identified as one of the risk factors contributing to late recurrence. However, a high pre-operative serum AFP level was also associated with late recurrence. Even without cirrhosis, HCC is prone to recurrence 2 years after PH when the serum AFP level was $>400 \mu\text{g/l}$.

An alternative interpretation of the current results is the association of cirrhosis and AFP. Previous studies reported that AFP could be used as a marker for liver fibrosis.^{23,24} AFP values were above the normal limit in 20–60% patients with liver cirrhosis even in the absence of HCC.²⁵ Liver cirrhosis is however more common in AFP-positive patients.²⁶ Cirrhotic patients with high AFP levels were more susceptible to develop HCC.¹¹ The above findings indicate that there is some underlying relationship between cirrhosis and AFP that influences the carcinogenesis of HCC. The present studies results would suggest that cirrhotic patients with an AFP level $>400 \mu\text{g/l}$ should be closely followed up beyond 2 years.

Table 1 Univariate analysis of factors associated with early and late recurrence

Variable		No recurrence (n = 194)	Early recurrence (n = 423)	P*	Late recurrence (n = 199)	P**
Median age (range, years)		52 (23–79)	51 (16–79)	0.179	51 (16–73)	0.854
Follow-up time (range, months)		63 (28–104)	45 (18–104)	0.017	58 (25–104)	0.004
Gender	Male	172	371	0.735	173	0.602
	Female	22	52		26	
HBsAg	Positive	164	356	0.905	178	0.15
	Negative	30	67		21	
HBeAg	Positive	81	175	0.929	67	0.098
	Negative	113	248		132	
Cirrhosis	Presence	133	329	0.014	163	0.002
	Absence	61	94		36	
AFP (ug/l)	≤400	146	279	0.021	113	<0.001
	>400	48	144		86	
PT (s)	≤13	101	242	0.232	100	0.720
	>13	93	181		99	
PLT (10 ⁹ /l)	≤100	42	73	0.194	53	0.249
	>100	152	350		146	
TBIL (μmol/l)	≤17.1	134	303	0.516	145	0.408
	>17.1	60	120		54	
ALB (g/l)	≤35	10	24	0.793	15	0.336
	>35	184	399		184	
ALT (U/l)	≤50	132	261	0.129	130	0.568
	>50	62	162		69	
HBV-DNA (I g, IU/ml)	≤4	127	261	0.369	148	0.055
	>4	67	162		51	
Intra-operative blood transfusion	Yes	24	75	0.094	17	0.217
	No	170	348		182	
Surgical margin (cm)	<2	57	163	0.028	78	0.041
	≥2	137	260		121	
Anatomical hepatectomy	Yes	113	273	0.134	130	0.149
	No	81	150		69	
Tumour diameter (cm)	≤5	144	257	0.001	129	0.043
	>5	50	166		70	
Tumour capsule	Complete	119	191	<0.001	101	0.035
	Incomplete	75	232		98	
MVI	Presence	80	251	<0.001	104	0.028
	Absence	114	172		95	
Edmondson–Steiner classification	I,II	122	230	0.048	109	0.103
	III,IV	72	193		90	

*Logistic regression analysis was performed on parameters between patients with early recurrence and patients with no recurrence.

**Logistic regression analysis was performed on parameters between patients with late recurrence and patients with no recurrence.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; HBeAg, hepatitis e antigen; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; MVI, microvascular invasion; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin.

Further attempts at curative treatment including re-resection, RFA and PEI have been shown to be effective treatments for recurrent HCC, offering a cumulative 5-year survival rate ranging from 40% to 64%.^{16,27} Although similar outcomes were achieved

within the present study, only 32% of patients with early recurrence and 46% of patients with late recurrence were suitable for such approaches. It has been suggested that salvage liver transplantation (SLT) is an efficacious treatment for patients with

Table 2 Multivariate analysis of risk factors for early and late recurrence of HCC patients

Variable	RR (95% CI)	SE	P
Early recurrence			
Tumour diameter (cm), >5	1.565 (1.048–2.358)	0.207	0.030
Tumour capsule, Incomplete	1.589 (1.097–2.309)	0.190	0.014
MVI, Presence	1.871 (1.304–2.693)	0.185	<0.001
Late recurrence			
Cirrhosis, presence	1.926 (1.171–3.199)	0.256	0.010
AFP (μg/l), >400	2.301 (1.482–3.606)	0.227	<0.001

AFP, alpha fetoprotein; CI, confidence interval; RR, risk ratio; SE: standard error.

recurrent HCC and should be considered when re-resection is not feasible.^{28,29} However, this optimistic suggestion needs to be further confirmed by an analysis of clinical outcomes. In the current study, no patients undergo SLT for recurrent HCC owing to the scarcity of donors or long waiting time, and the majority of patients with recurrence received TACE or conservative treatment with sorafenib.

In conclusion, the present study suggests that early and late intrahepatic recurrences of solitary HCC after curative PH have distinct factors, and the pattern of recurrence and the probability of curative treatments after recurrence are the best determinants for the prognosis. The strength of this study lies in the relative large sample size involving 816 patients with solitary HCC tumours who underwent curative resection.

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Conflict of interest

None declared.

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